FUNCTIONAL ROLE OF NEUROPEPTIDE Y IN THE CENTRAL NERVOUS SYSTEM, M. Heilig, Dept. of Clinical Neuroscience, Karolinska Institute, 17176 Stockholm, Sweden.

Neuropeptide Y (NPY), isolated by Tatemoto and Mutt in 1982, is the prototypical member of the NPY / pancreatic polypeptide (PP) family. The amino acid (a.a.) sequence of NPY is highly conserved, suggesting a physiological importance of this peptide. In the periphery, NPY is a well established co-transmitter of the sympathetic nervous system, and participates in peripheral cardiovascular control. In the central nervous system (CNS), NPY is present in widespread neuronal populations, i.e. ascending brain stem projections, intrahypothalamic pathways, and local interneurons within telencephalic areas. Two prominent CNS actions of NPY represent attractive targets for drug development: 1. Stimulation of food intake, in particular that of carbohydrates, mediated through hypothalamic mechanisms, and possibly controlled by the endogenous ob protein, leptin; 2. Reduction of experimental anxiety, mediated through the amygdaloid complex, and possibly representing an endogenous counterbalance to the major endogenous stress / fear signal, corticotropin-releasing hormone (CRH). Physiological and pharmacological actions of NPY are mediated through heterogeneous receptor population, suggesting a potential for precise targeting with novel drugs. Several receptor subtypes for NPY and related peptides have been cloned and characterized, i.e. those corresponding to the original Y1 / Y2 subdivision proposed on the basis of ligand affinity studies, in which the full a.a. sequence of NPY was required for activation of Y1 receptors, while Y2 receptors could also be activated by truncated C-terminal fragments. Peripheral pressor effects of NPY, as well as anti-anxiety actions of central NPY seem to be mediated through activation of Y1-type receptors. In hippocampus, actions of NPY on neuronal excitability possibly related to memory mechanisms are exerted though Y2 receptors. The receptor subtype mediating feeding effects of NPY is less clear, with some evidence to suggest the possibility that it differs both from conventional Y1 and Y2 receptors. Ongoing isolation and characterization of new NPY-receptor clones will provide information whether feeding and anxiety effects of central NPY-receptor activation can be separated, a likely prerequisite for development of therapeutically useful drugs targeting these functions.

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